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ACYCLOVIR- THE BEST COMBATANT IN TREATING *HERPES ZOSTER*

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Abstract:

Acyclovir is a drug of choice for the treatment of a Virus strain called as Herpes. Particularly a Virus called as *Herpes zoster* which is a reactivation of latent *Varicella zoster virus*. This virus can cause many diseases and complicated complications. This may start in the mouth and can produce a neuralgia(post-herpetic neuralgia). This Virus has a high rate of morbidity i.e. has a higher chance of causing death to the person affected with it. There has been a lot of papers on the effects of the drug on the virus and where the Herpes zoster viruses can occur and then try to enumerate the treatment. Also in this paper I would like to tell about why Acyclovir is the best drug to combat the Herpes virus from our community.

Key words: Acyclovir, Valaciclovir, Herpes simplex virus, Herpes zoster.

Abbreviations:

HSV-herpes simplex virus

VZV-varicella zoster irus

HZO-herpes zoster ophthalmicus

PHN- post-herpetic neuralgia

What is Acyclovir?

Acyclovir is a guanosine analogue antiviral drug .One of the most commonly used antiviral drugs.

It is primarily used for the treatment of herpes simplex virus infections, as well as in the treatment of Varicella zoster (chickenpox) and herpes zoster (shingles).

It is marketed under the following names

Cyclovir,

Herpex,

Acivir,

Acivirax,

Zovirax,

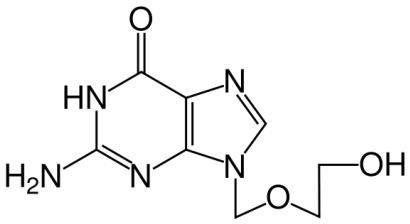
Zoral,

Xovir and

Imavir.

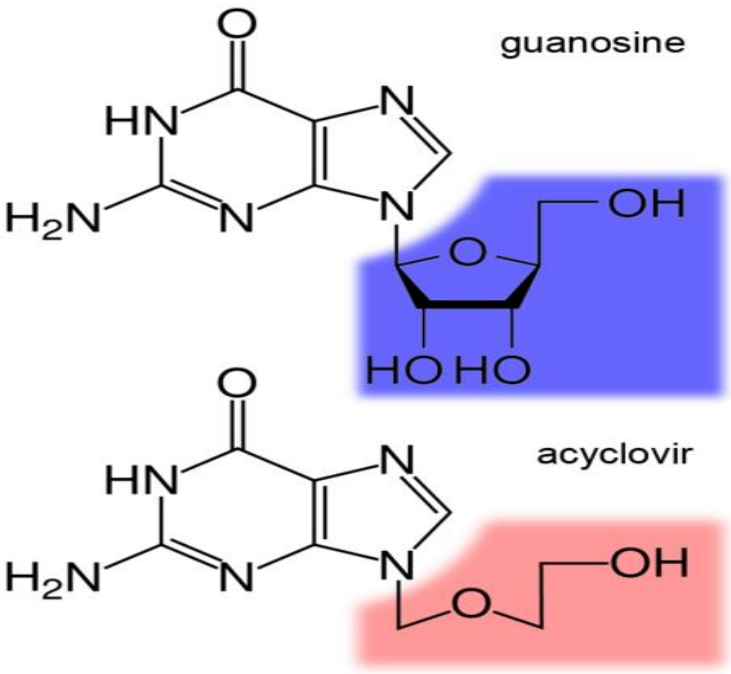
Chemical name of this drug is 2-Amino-1,9-dihydro-9-2-hydroxyethoxymethyl-6*H*-purin-6-one.

The composition of the drug or the structure of the drug is as follows.



Structure of Acyclovir.

This structure is very similar to guanosine expect for a small deletion in the **<u>OH</u>** group in the drug acyclovir hence the name of *Guanosine analog.*



The Structural Differences Between Guanosine and Acyclovir.

As we can see, in the highlighted area that the drug and guanosine differs only in the attachment of two hydroxyl groups to the monovalent oxygen.

Mechanism of Action.

The acyclovir monophosphate (acyclo-GMP) is subsequently converted to acyclovir triphosphate (acyclo-GTP) by cellular enzymes. Acyclo-GTP persists in HSV-infected cells for many hours after acyclovir is removed from the medium. The amounts of acyclo-GTP formed in HSV-infected cells are 40 to 100 times greater than in uninfected Vero cells.

Acyclo-GTP acts as a more potent inhibitor of the viral DNA polymerases than of the cellular polymerases. The DNA polymerases of HSV-1 and HSV-2 also use acyclo-GTP as a substrate and incorporate acyclo-GMP into the DNA primer-template to a much greater extent than do the cellular enzymes. The viral DNA polymerase binds strongly to the acyclo-GMP-terminated template, and in thereby inactivated. Acyclovir has low toxicity for the Normal host cells, this selectivity is due to the ability of these viruses to code for a viral thymidine kinase capable of phosphorylating acyclovir to a monophosphate. This capability is essentially absent in uninfected cells.

Resistance

Resistance to acyclovir is rare, but is more common in patients on chronic antiviral prophylaxis (transplant recipients, people with acquired immunodeficiency syndrome due to HIV infection). Mechanisms of resistance in HSV include deficient viral thymidine kinase; and mutations to viral thymidine kinase and/or DNA polymerase, altering substrate sensitivity. Acyclovir has also shown cross-resistance with valaciclovir and famciclovir.

Pharmacokinetics

Acyclovir is poorly water soluble and has poor oral bioavailability (15– 30%) Hence intravenous administration is necessary if high concentrations are required. When orally administered, peak plasma concentration occurs after 1–2 hours. Acyclovir has a high distribution rate; protein binding is reported to range from 9 to 33%.

The elimination half-life of acyclovir is approximately 3 hours. It is renally excreted, partly by glomerular filtration and partly by tubular secretion. The poor oral bioavailability may also be improved by administering valaciclovir, which has an oral bioavailability of about 55%. Valaciclovir is then converted to acyclovir by esterases via hepatic first-pass metabolism.

Clinical Uses

Indications.

Acyclovir is indicated for the treatment of HSV and VZV infections, including:

- Genital herpes simplex (treatment and prophylaxis)
- Herpes simplex labialis (cold sores)
- Herpes zoster (shingles)
- Acute chickenpox in immunocompromised patients
- Herpes simplex encephalitis
- Acute mucocutaneous HSV infections in immunocompromised patients
- Herpes simplex keratitis (ocular herpes)
- Herpes simplex blepharitis (not to be mistaken with ocular herpes)
- Prophylaxis against herpes viruses in immunocompromised patients (such as patients undergoing cancer chemotherapy)

Dosage And Routes.

Acyclovir is commonly marketed as tablets (200 mg, 400 mg, 800 mg and 1 gram), topical cream (5%), intravenous injection (25 mg/mL) and ophthalmic ointment (3%).

- Cream preparations are used primarily for labial herpes simplex.
- The ophthalmic ointment preparation is only used for herpes simplex keratitis.
- The intravenous injection is used when high concentrations of aciclovir are required such as in HSV encephalitis, Acute retinal necrosis, and disseminated zoster disease.

Following are evidences and roles of acyclovir in the treatment of various disorders and systemic diseases ranging from neonatal development to the adult treatment.

Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes[10]

Infants surviving neonatal HSV disease with CNS involvement had improved neurodevelopmental outcomes when they received suppressive therapy with oral acyclovir

for 6 months. (Funded by the National Institute of Allergy and Infectious

Diseases; CASG 103 and CASG 104 ClinicalTrials.gov numbers, NCT00031460 andNCT00031447, respectively.)[10] The outcomes of neonatal herpes simplex virus (HSV) disease are dependent on the extent of the disease[11].Approximately30% of babies with disseminated disease die, but only 20% of survivors have neurologic sequelae[12]. In contrast, only 6% of babies with central nervous system (CNS) disease die, but approximately 70% have permanent neurologic impairment[12].

Skin, eye, and mouth disease is not associated with death, and neurologic impairment is rare with this manifestation of neonatal herpes[13]. HSV establishes latency in sensory ganglia, with periodic reactivation and recurrence of localized disease[14,15]. Whether the virus subclinically reactivates in the brain after neonatal HSV disease is not known. If reactivation in the brain does occur, it could contribute to the serious neurologic sequelae associated with neonatal HSV disease with CNS involvement, as has been suggested[16]. Antiviral suppressive therapy prevents the recurrence of localized disease in persons with genital[17-20]or orolabial[21,22] HSV infection. The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) conducted parallel, identical, phase 3, placebo-controlled studies of oral acyclovir suppressive therapy after neonatal HSV disease to determine the efficacy and safety of long-term antiviral administration during infancy.

Many clinicians assumed that oral acyclovir would be efficacious, on the basis of the results of small, uncontrolled studies, further challenging the conduct of randomized, controlled trials. The long-term follow-up required to assess neurodevelopmental outcomes also affected the ability to follow all the enrolled infants for the primary protocol end point.

Previous uncontrolled studies have suggested that acyclovir therapy may be associated with neutropenia[12,23] In the current placebo-controlled studies, neutropenia was not more likely to develop in infants receiving acyclovir than in infants receiving placebo. Babies with skin, eye, and mouth disease can benefit because this therapy helps to prevent skin recurrences, whereas babies with CNS disease may have additional benefit with respect to neuro developmental outcomes. There are no controlled data that suggest that suppressive therapy administered longer than 6 months or with the use of higher doses of oral acyclovir is beneficial. An extemporaneously compounded oral solution of valacyclovir has not been sufficiently studied in neonates and young infants to warrant its use instead of oral acyclovir for antiviral suppression.

Acyclovir in Early Herpes Zoster Ophthalmicus:

Poor systemic absorption has limited the, efficacy of early oral acyclovir in herpes zoster ophthalmicus (HZO).Aqueous humour levels are substantially higher if the drug is administered topically to the eye. A multicentre open randomised study was performed to compare the ocular prophylactic effects of topical and oral acyclovir. Fifty-seven patients with HZO within 72 hours of the onset of rash received either topical acyclovir ointment or800 mg oral acyclovir, both 5 times daily for 7 days, and were followed for 12 months. Patients receiving ointment were significantly more likely to have ocular complications ($p<0.02$) and anterior uveitis was significantly more frequent ($p<0.01$) and severe ($p<0.0l$). Corneal hypoaesthesia was significantly more frequently ($p<0.05$) and severe ($p<0.02$) at 1 month. From 2 weeks patients receiving ointment were more likely to have pain and at all times their pain was more severe, but these differences were not statistically significant. In spite of its apparently better penetration topical acyclovir appears to have no prophylactic value in the management of early HZO.

Management of HZO remains controversial. Recent attention has centred on the role of antivirals and in particular acyclovir in management and prophylaxis. There is also a role for topical steroids but the precise relationship between these two therapeutic options remains unclear[24].Two studies have reported prophylactic effects in the eye of oral acyclovir in HZO provided it is commenced within 72 hours of the onset of rash[25,26]. Results were somewhat conflicting, with one study showing an early and one a late effect. A retrospective case control investigation failed to detect a significant therapeutic effect. Double-masked placebo-controlled studies on the effect of acyclovir on pain in HZOU, and in nonophthalmic herpes zoster have also produced conflicting results. All have shown a prophylactic effect on pain but this has either been early or late. Because of these studies the use of early oral acyclovir has become widespread, although several ophthalmologists do not use oral acyclovir routinely for HZO because of the relatively high cost and doubts about efficacy[27].

Oral acyclovir is only partially absorbed, with plasma levels which plateau at doses above 800 mg and are only slightly higher than the mean effective dose (EDso) for most strains of varicella zoster virus. It seems likely that the benefits of oral acyclovir are limited by poor

systemic absorption. Aqueous humour levels are substantially higher if the drug is administered topically to the eye and this formulation may offer better ocular efficacy than the oral drug as well as being considerably cheaper[28-31].

Oral acyclovir prophylaxis against herpes simplex virus in non-Hodgkin lymphoma and acute lymphoblastic leukaemia patients receiving remission induction chemotherapy[32]: Forty-one patients receiving remission induction chemotherapy with vincristine, adriamycin and prednisolone (VAP) for high grade lymphoma or acute lymphoblastic leukaemia were entered into a double blind, placebo controlled trial of oral acyclovir prophylaxis against herpes simplex virus (HSV) infection. The dose of acyclovir was 200mg four times daily for the duration of chemotherapy (six weeks). Of the 40 evaluable patients, 20 were randomised to each arm. Prophylactic oral acyclovir significantly reduced the incidence of clinical HSV infection from 60% on placebo to 5% acyclovir ($P<0.001$), and the incidence of viral isolates from 70% on placebo to 5% on acyclovir ($P<0.001$)[32].

Management of herpes zoster in PHN:

Postherpetic neuralgia is a nerve pain due to damage caused by the VZV. Typically, the neuralgia is confined to a dermatomic area of the skin and follows an outbreak of herpes zoster in that same dermatomic area. The neuralgia typically begins when the herpes zoster vesicles have crusted over and begun to heal, but it can begin in the absence of herpes zoster.

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